for example, at page 9, lines 1-14. Claim 28 is amended further by the addition of language specifying the structure of the CD30-L polypeptide in terms of the DNA sequences that encode the polypeptide. This amendment is supported in the specification, for example, at page 11, line 32 to page 12, line 3. The binding of CD30-L to the CD30 polypeptide recited in amended claims 27 and 28 is supported throughout the specification, for example, at page 2, lines 35-36; page 3, lines 16-17; page 4, lines 20-22; page 7, lines 31-33; page 12, line 29 to page 14, line 11; page 22, lines 3-4; and at page 25, line 25 to page 30, line 21.

The amendment to claim 29 consists of removing repetitious language that already is present in amended claim 27, from which claim 29 depends.

The amendments to claim 32 consist of amending the claim language to recite particular amino acid sequences corresponding to soluble murine or human CD30-L. This amendment is supported in the specification as described above for similar amendments to claims 27 and 28.

Claim 36 has been amended to change its dependency from claim 34 to claim 33 because claim 34 has been cancelled.

Claim 62 has been amended to delete "saporin toxin," and dependent claim 70 reciting "saporin toxin" has been added to the application. Support for new claim 70 is found, for example, in original claim 62, and in the specification at page 15, lines 8-10.

Claim 68 has been amended to change its dependency from cancelled claim 67 to claim 50, and has been amended further to delete the phrase "fragment of human," as the deleted language was deemed unnecessary for defining the scope of the claim.

The amendments to claim 69 include adding the term "soluble" to modify "CD30-L," and of amending the claim language to recite amino acid sequences corresponding to soluble forms of murine or human CD30-L. These amendments to claim 69 are supported as described above for similar amendments to claims 27, 28 and 32.

References in IDS

The examiner has stated in Paper No. 11 that two of the references cited in the IDS filed 1/3/2002 were not found in the priority documents, namely Dallenbach et al. and Stein et al., and that the Pfreundschuh et al. citation had been crossed out because no translation had been provided. Applicants believe that the examiner had intended to refer to the IDS that was mailed 11/14/2001 rather than 1/3/2002. Copies of the Dallenbach et al. and Stein et al. papers are attached hereto. A translation of the Pfreundschuh et al. paper is presently being pursued.

Objection to the Specification

The examiner has indicated in paragraph 4 of Paper No. 11 that the specification lacks antecedent basis for the method step recited in original claim 29 and has suggested that the specification be corrected accordingly. Applicants do not agree that such correction is warranted. There is no requirement that the exact language appearing in a claim appear verbatim in the specification. 37 CFR 1.75(d)(1) requires only that the meaning of the terms used in the claims "find clear support or antecedent basis" in the specification. Support for original claim 29 is found throughout the specification, for example, at page 14, lines 16-28, and page 15, lines 29 to page 16, line 5. This disclosure clearly apprises those skilled in the art of the meaning of the terms and phrases in original claim 29. Accordingly, the examiner is asked to withdraw the requirement that the specification be amended.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 62 has been rejected under 35 U.S.C. § 112, second paragraph, in view of the examiner's contention that the Markush group recited in this claim is indefinite because the group recites saporin toxin, ribosomal inactivating proteins and mycotoxin. The examiner asserts that mycotoxin and saporin toxin are ribosomal inactivating proteins, and asserts also that "a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite." The examiner provides no source of authority for this assertion. The applicants do not agree that "mycotoxins" should be classified as a species of "ribosomal inactivating proteins." The term "mycotoxin" means a toxin that is derived from a fungus (see definition, attached as "Exhibit A"). The examiner has presented no evidence that all mycotoxins are ribosomal inactivating proteins. Claim 62 has been amended to delete "saporin toxin," and a dependent claim that recites saporin toxin has been added to the application. In view of these amendments and comments, the examiner is respectfully asked to remove the rejection of claim 62 under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 27-30, 32-34 and 50-69 have been rejected under 35 U.S.C. § 112, first paragraph in view of the examiner's position that the specification is not enabling for conjugates comprising the broad categories of CD30L polypeptides recited in these claims. However, the examiner has indicated at page 4 of Paper No. 11 that the claims would be enabled if further limitations were added to the claim language. Accordingly, the claims have been amended to limit the CD30L polypeptides to soluble forms of CD30L that are capable of binding CD30, these CD30L polypeptides being based on specific SEQ ID NOS that are present in the specification, and

moreover the target to which these conjugates is to be delivered has been limited to malignant cells. The examiner objected also to claim language pertaining to "fragments." The term "fragment" has been eliminated from the claims as this terminology was deemed unnecessary.

Claims 27-30, 32-45 and 50-69 have been rejected under 35 U.S.C. § 112, first paragraph in view of the examiner's position that the claims contain subject matter that was not sufficiently described in the specification. As amended, the claims now are limited to conjugates that employ soluble CD30L polypeptides defined according to both function, i.e., the ability to bind CD30, and structure, i.e., by reference to particular CD30L sequences that are disclosed in the application. This ground for rejection is now believed to be moot. The examiner therefore is respectfully requested to remove the rejections based on 35 U.S.C. § 112, first paragraph.

Filing Date of the Instant Claims

The examiner has asserted that the present claims are entitled to a filing date no earlier than 04/12/1994. In paragraph no. 8 of paper No. 11, she has listed six of the prior applications from which the present application claims priority. However, she appears to have overlooked a seventh application from which the subject application also claims priority, namely International Application PCT/US93/04926 (WO 93/24135), which was filed May 25, 1993 (see the specification at page 1, lines 17-18).

Rejections under 35 U.S.C. § 102

Claims 27, 38, 50 and 61-63 have been rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent No. 5,165,923. The examiner notes that the present specification defines "CD30-L" as being "a genus of polypeptides which are capable of binding CD30" (specification at page 4, lines 12-13). The examiner argues that this definition for "CD30-L" encompasses an antibody that binds specifically with CD30. She notes further that U.S. Patent No. 5,165,923 teaches conjugates comprising toxins and antibodies specific for CD30 and the use of these conjugates to treat Hodgkin's disease and lymphomas associated with CD30+ lymphocytes. The claims as amended are limited to the use of conjugates comprising soluble CD30-L polypeptides based on sequences that are not disclosed in U.S. 5,165,923. Accordingly, this reference does not anticipate the invention as claimed, and the examiner is therefore requested to withdraw the rejection of claims 27, 38, 50 and 61-63 under 35 U.S.C. § 102 over U.S. 5,165,123.

Rejections under 35 U.S.C. § 103(a)

Rejections over U.S. 5,165,923 in view of WO 92/00762

In paragraph 9 of Paper No. 11, claims 27, 38, 50, 58-63 and 65 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,165,923 in view of WO 92/00762. U.S. 5,165,923 is discussed above. WO 92/00762 is asserted to teach targeting toxins to receptors via the use of conjugates comprising various toxins and an antibody to the receptor or a natural ligand for the receptor. However, WO 92/00762 does not disclose the CD30L sequences recited in claims 27, 38, 50, 58-63 and 65 as now amended. If one were to substitute the antibody taught by U.S. 5,165,923 for the antibody or natural ligand taught by WO 92/00762, the result would not constitute the invention claimed herein. Thus, the present claims are not obvious in view of the combination of U.S. 5,165,923 in view of WO 92/00762, and the examiner therefore is respectfully requested to remove this ground for the rejection of claims 27, 38, 50, 58-63 and 65 under 35 U.S.C. § 103(a).

Rejections over U.S. 5,165,923 in view of WO 92/00762 and U.S. 5,541,287

In paragraph 10 of Paper No. 11, claims 51, 54-57, 59, 62, 64 and 66 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,165,923 in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63 and 65, and further in view of U.S. 5,541,287. The examiner has noted that the '287 patent teaches toxin conjugates for use in cancer therapy, and that the toxins disclosed in the '287 patent include some of the toxins recited in the rejected claims. The examiner has asserted that it would be obvious to substitute the toxins taught by the '287 patent for the therapeutic agents derived by combining the teachings of U.S. 5,165,923 and WO 92/00762. However, as explained above, neither U.S. 5,165,923 nor WO 92/00762 discloses the soluble CD30L molecules to which the conjugates described in amended claims 51, 54-57, 59, 62, 64 and 66 are limited. Accordingly, even if one combined the teachings of U.S. 5,165,923, WO 92/00762 and U.S. 5,541,287 as proposed by the examiner, the resulting methods would not correspond to the invention described in claims 51, 54-57, 59, 62, 64 and 66. The examiner is therefore asked to remove this ground for the rejection of claims 51, 54-57, 59, 62, 64 and 66 under 35 U.S.C. § 103(a) in view of the combination of U.S. 5,165,923, WO 92/00762 and U.S. 5,541,287.

Rejections over U.S. 5,165,923 in view of WO 92/00762 and U.S. 5,208,020

In paragraph 11 of Paper No. 11, claims 56, 57 and 59 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,165,923 in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63 and 65, and further in view of U.S. 5,208,020. The examiner has noted that the '020 patent teaches a method of

delivering a conjugate comprising a therapeutic agent and maytansinoids or antibodies to selectively kill specific cell populations, such as tumor cells. She has asserted further that it would be obvious to substitute the cytotoxic agents taught by the '020 patent for the toxins taught by U.S. 5,165,923 and WO 92/00762 to create an effective immunotoxin to target $CD30^+$ tumor cells. However, such substitution would not result in the methods claimed in claims 56, 57 and 59 because these claims involve conjugates comprising soluble CD30L polypeptides that are not disclosed in the cited references. Accordingly, claims 56, 57 and 59 are not obvious under 35 U.S.C. § 103(a) over U.S. 5,165,923 in view of WO 92/00762 and U.S. 5,208,020, and the examiner therefore is respectfully requested to remove this ground for the rejection of claims 56, 57 and 59.

Rejections over U.S. 5,165,923 in view of WO 92/00762 and U.S. 5,019,368

In paragraph 12 of Paper No. 11, claims 50-51, 56-59 and 66 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,165,923 in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63 and 65, and further in view of U.S. 5,019,368. The examiner has asserted that the '368 patent teaches methods for delivering a conjugate comprising a therapeutic agent and antibodies to selectively kill cells such as tumor cells. However, even if one were motivated to combine these three references as was done by the examiner, the resulting method would not correspond to the invention described in amended claims 50-51, 56-59 and 66. Claims 50-51, 56-59 and 66, as amended, are limited to conjugates that comprise soluble CD30L polypeptides defined according to sequences that are not disclosed in U.S. 5,165,923, WO 92/00762 or U.S. 5,019,368. The examiner is therefore asked to remove this ground for the rejection of claims 50-51, 56-59 and 66 under 35 U.S.C. § 103(a) over the combination of U.S. 5,165,923, WO 92/00762 and U.S. 5,019,368.

Rejections over U.S. 5,165,923 in view of WO 92/00762 and U.S. 4,867,962

In paragraph 13 of Paper No. 11, claims 50-53, 54-57, 59, 64 and 66 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,165,923 in view of WO 92/00762 as applied earlier to claims 27, 38, 50, 58-63 and 65, and further in view of U.S. 4,867,962. The examiner has noted that the '962 patent teaches the delivery of a therapeutic agent to a desired target site by attaching the agent to an antibody. However, even if one skilled in the art were motivated to combine these three references as was done by the examiner, the resulting methods would not correspond to the invention described in the rejected claims, because none of these references disclose the soluble CD30L polypeptides that are used to form the conjugates that are recited in amended claims 50-53, 54-57, 59, 64 and 66. The examiner therefore is respectfully requested to remove the rejection of claims 50-53,

54-57, 59, 64 and 66 under 35 U.S.C. § 103(a) in view of the combination of U.S. 5,165,923, WO 92/00762 and U.S. 4,867,962.

Rejections over U.S. 5,165,923 in view of WO 92/00762 and WO 93/24135

In paragraph 14 of Paper No. 11, claims 28-30, 32-46 and 67-69 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,165,923 in view of WO 92/00762 as applied earlier to claims 27, 38, 50, 58-63 and 65, and further in view of WO 93/24135. Claims 50-66 are not included in this rejection. Claim 46 is not under consideration because it was cancelled in the amendment submitted 11/20/2001. The examiner has noted that WO 93/24135 teaches soluble CD30L polypeptides.

The examiner has failed to make a *prima facie* case of obviousness over the cited combination of references. The appropriate standard for combining a group of references under 35 U.S.C. § 103 was recently restated by the Federal Circuit in *In re Lee* (61 USPQ2d 143 (2002); copy attached as Exhibit B). In *In re Lee*, the examiner had rejected the claims as obvious over the combination of a U.S. patent describing a television menu display and the manual for a video game, stating that one skilled in the art would have been motivated to combine these teachings because the element extracted from the video game manual could "be used in many different devices," and was "user friendly and function[ed] as a tutorial." The Board of Patent Appeals and Interferences had approved the examiner's reliance on "common sense," and had held that a "specific hint or suggestion" of motivation to combine was not required (*In re Lee* at page 1432). The Federal Circuit disagreed, stating that "the factual question of motivation is material to patentability and could not be resolved on subjective belief and unknown authority" (*In re Lee* at 1434).

When the standard set forth by *In re Lee* is applied here, it is apparent that one skilled in the art would not have been motivated to combine the three references cited by the examiner. The examiner cites U.S. 5,165,923 as disclosing the treatment of Hodgkin's disease and lymphomas associated with $CD30^+$ lymphocytes by administering conjugates comprising toxins that are linked to antibodies against CD30. The examiner has proposed that it would be obvious to one skilled in the art to substitute the present CD30L polypeptides for the anti-CD30 antibodies of U.S. 5,165,923. However, the '923 disclosure does not teach or suggest that molecules other than antibodies should be substituted for the anti-CD30 antibodies described therein. The disclosure of WO 92/00762 teaches targeted toxin conjugates comprising a toxin, but does not disclose conjugates that include the soluble CD30L polypeptides that are recited in amended claims 28-30, 32-45 and 67-69. WO 93/24135 does not teach or suggest that soluble CD30L should be ligated to the toxins

disclosed in the '923 patent or in WO 92/00762 for administration to $CD30^+$ malignant cells. Accordingly, the rejection of claims 28-30, 32-45 and 67-69 under U.S.C. § 103(a) over U.S. 5,165,923 in view of WO 92/00762 and WO 93/24135 should be withdrawn.

Even had the examiner set forth a valid *prima facie* case for rejection of claims 28-30, 32-45 and 67-69 under U.S.C. § 103(a) over U.S. 5,165,923 in view of WO 92/00762 and WO 93/24135, this rejection still is improper because WO 93/24135 is not available as prior art against the claimed invention as asserted by the examiner. All of the persons named as inventors on WO 93/24135 are among the applicants in the present application. WO 93/24135 was published on 12/09/1993, which is less than a year before the filing date of parent application 08/225,989. Accordingly, WO 93/24135 is not prior art under 102(b) against the present application, therefore there is no statutory bar.

The examiner has cited the WO 93/24135 application for teaching soluble CD30L polypeptides, and various properties of such polypeptides that she considers to be pertinent to the invention described in claims 28-30, 32-45 and 67-69. To the extent that WO 93/24135 contains material that is pertinent to the patentability of these claims, the applicants should be recognized as having invented such material prior to the publication of WO 93/24135. "In the case of a reference, it is fundamental that it is valid for what it discloses and if the applicant establishes priority with respect to that disclosure, and there is no statutory bar, it is of no effect at all." *In re Stempel*, 113, USPQ 77, 81 (CCPA 1957); copy attached as "EXHIBIT C." In *In re Stempel*, the applicants had established by affidavit that they had invented the subject matter disclosed in an allegedly anticipatory reference prior to the publication date of the reference. In the present case, no affidavit is necessary because the applicants who are named as inventors on the cited reference have already declared that the subject matter in the WO 93/24135 application is their invention, and thus have demonstrated priority to a date prior to the publication of WO 93/24135 for the subject matter relied upon by the examiner. In view of these circumstances, the subject matter that the examiner has cited from WO 93/24135 is not prior art to the instantly claimed invention. The court in *In re Stemplel* held that "under the law all the applicant can be required to show is priority with respect to so much of the claimed invention as the references happens to show." (*Id.*) Since WO 93/24135 is not properly cited as a reference, the examiner is respectfully requested to withdraw the rejection of claims 28-30, 32-45 and 67-69 under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,165,923 in view of WO 92/00762 and WO 93/24135.

CONCLUSIONS

Claims 27-30, 32-45 and 50-70 are currently under consideration in the application and stand rejected under 35 U.S.C. § 112, first and second paragraphs, § 102 or § 103. It is believed that these grounds for rejection have been overcome by virtue of the amendments and comments set forth above. Accordingly, the applicants believe that the claims as amended are in condition for allowance and notification to that effect is respectfully requested. If further issues remain in this application, the examiner is asked to contact the undersigned at her direct dial number given below.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on the date indicated below.

Date: Oct 18, 2002

D. F. Lindholm

Appendix to Amendments filed October 18, 2002
(marked up version of claims amended by the attached Amendment)

In the Specification:

-- This application is a divisional of U.S. application Serial No. 09/079,785, filed May 15, 1998, [currently allowed] now U. S. Patent 6,143,869, which is a divisional of U.S. application Serial No. 08/580,014, filed December 20, 1995, now U.S. Patent 5,753,203, which is a divisional of U.S. application Serial No. 08/225,989, filed April 12, 1994, now U.S. Patent 5,480,981, which is a continuation-in-part of U.S. [A]application Serial No. 07/966,775, filed [on] October 27, 1992, [currently pending] now abandoned, which is a continuation-in-part of U.S. [A]application Serial No. 07/907,224, filed [on] July 1, 1992, now abandoned, which is a continuation-in-part of U.S. [A]application Serial No. 07/899,660, filed [on] June 15, 1992, now abandoned, which is a continuation-in-part of U.S. [A]application Serial No. 07/892,459, filed [on] June 2, 1992, now abandoned, which is a continuation-in-part of U.S. [A]application Serial No. 07/889,717, filed [on] May 26, 1992, now abandoned. Priority is also claimed from International Application PCT/US93/04926. --

In the Claims:

27. (amended) A method of delivering a therapeutic agent to $CD30^+$ malignant cells, comprising contacting said cells with a conjugate comprising one or more therapeutic agents attached to a soluble CD30 ligand (CD30-L) polypeptide, wherein said soluble CD30-L polypeptide is capable of binding a CD30 polypeptide consisting of amino acids 19-390 of SEQ ID NO:1, and further wherein the amino acid sequence of said CD30-L is at least 90% identical to amino acids 49-220 of SEQ ID NO:19 or amino acids 47-215 of SEQ ID NO:23.

28. (amended) A method of delivering a therapeutic agent to $CD30^+$ malignant cells, comprising contacting said cells with a conjugate comprising one or more therapeutic agents attached to a soluble CD30-L polypeptide, wherein said soluble CD30-L polypeptide is [a soluble fragment of the human CD30-L of SEQ ID NO:8] capable of binding a CD30 polypeptide consisting of amino acids 19-390 of SEQ ID NO:1 and further wherein said soluble CD30-L is encoded by a DNA that is capable of hybridizing under conditions of moderate stringency to the nucleotide sequence of SEQ ID NO:22, wherein said hybridization conditions comprise hybridizing at 55° in 5 X SSC.

29. (amended) A method according to claim 28, wherein [said cells are malignant and] said conjugate is administered in an effective amount to a human afflicted with said malignant cells.

32. (amended) A method according to claim 27, wherein said soluble CD30-L polypeptide is in the form of an oligomer comprising two or more soluble CD30-L polypeptides, wherein the soluble CD30-L polypeptides are each selected from the group consisting of:

a) [the murine CD30-L] amino acids 49-220 of SEQ ID [NO:6] NO:19; and

b) [the murine CD30-L] amino acids z-215 of SEQ ID [NO:19] NO:23, wherein z is amino acid 44, 45, 46 or 47 of SEQ ID NO:23[;

c) the human CD30-L of SEQ ID NO:8;

d) the human CD30-L of SEQ ID NO:23; and

e) a fragment of the CD30-L of (a), (b), (c), or (d), wherein said fragment binds CD30].

62. (amended) A method according to claim 61, wherein the toxin is selected from the group consisting of ricin, abrin, [saporin toxin,] diptheria toxin, *Pseudomonas aeruginosa* exotoxin A, ribosomal inactivating proteins and a mycotoxin.

68. (amended) A method according to claim [67]50, wherein the soluble [fragment of human] CD30-L polypeptide is fused with a human IgG1 Fc region.

69. (amended) A method according to claim 50, wherein the soluble CD30-L polypeptide is in the form of an oligomer comprising two or more soluble CD30-L polypeptides, wherein the soluble CD30-L polypeptides are each selected from the group consisting of:

a) [the murine CD30-L] amino acids 49-220 of SEQ ID [NO:6] NO:19; and

b) [the murine CD30-L] amino acids z-215 of SEQ ID [NO:19] NO:23, wherein z is amino acid 44, 45, 46 or 47 of SEQ ID NO:23[;

c) the human CD30-L of SEQ ID NO:8;

d) the human CD30-L of SEQ ID NO:23; and

e) a fragment of the CD30-L of (a), (b), (c), or (d), wherein said fragment binds CD30].